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Clinico-pathologic study of pulmonary carcinoid tumours — A retrospective analysis and review of literature

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Summary
Objective: To determine the characteristic clinico-pathologic features of pulmonary carcinoid tumours in India.
Methods: Retrospective analysis of the clinico-pathologic and radiologic data of patients with pulmonary carcinoid tumours from the department of Pulmonary Medicine of the Christian Medical College, a tertiary care teaching hospital in Southern India, over a study period of 3 years (2001–2004).
Results: There were 25 cases of pulmonary carcinoid tumours: typical 22 (88%) and atypical 3 (12%). The ratio of female to male was 0.8:1. There were 3 smokers (all of whom were males) in the typical carcinoid group and none in the atypical carcinoid group. Haemoptysis and cough were the commonest presenting symptoms. The common radiologic findings were post-obstructive pneumonitis or atelectasis, and mass lesion. Carcinoid syndrome was not present in any patient. Most of the tumours were central ($n = 23$; 92%) and in the main bronchi ($n = 13$; 52%). The most common site was the right main bronchus ($n = 9$; 36%). Diagnosis was made by flexible bronchoscopy and bronchial biopsy in 23 patients (92%). The tumour bled significantly following biopsy in most patients; however, there was no mortality, and only 1 patient required blood transfusion. Surgical option was offered to most; 13 patients (52%) had pneumonectomy and 4 patients (16%) had lobectomy. A review of large series from the literature is also presented.
Conclusion: The clinico-pathologic and radiologic features of pulmonary carcinoid tumours are presented. We report the first series of pulmonary carcinoid tumours from India.

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Introduction

Bronchial carcinoid tumours are low-grade malignant neoplasm comprised neuroendocrine cells. They account for 1–5% of all lung tumours.[1,2] About 90% of the carcinoid tumours are referred to as ''typical'' carcinoid tumours, and are well differentiated with rare mitoses, pleomorphism, and necrosis.[3,4] The remaining 10% are designated ''atypical'' carcinoids, and are characterised histologically by increased mitotic activity, nuclear pleomorphism and disorganisation. The present retrospective study was conducted to determine the characteristic clinico-pathologic and radiologic features of carcinoid tumours in India. To the best of our knowledge this is the first case series of pulmonary carcinoid tumours published from India.

Materials and methods

We reviewed the medical records of 25 patients with pulmonary carcinoid tumours diagnosed and treated in the department of Pulmonary Medicine of the Christian Medical College, Vellore, a major teaching hospital in South India, over a 3-year period (2001–2004). The data analysed included patient's age and sex, smoking history, presenting symptoms, radiologic appearance, mode of diagnosis, location of the tumour, tumour spread, immuno-histochemical findings, and methods of treatment. Patients were also analysed for comparison by type of tumour – typical or atypical.

Appropriate measures were undertaken to ensure that patient confidentiality is maintained and the study was the hospital board.

Results

Among the 25 patients with carcinoid tumour were 14 males and 11 females; aged 14–56 years (mean age 38.3 years). The ratio of female to male patients was 0.8:1. Histopathologically, 22 patients (88%; 13 males and 9 female patients; age range: 14–56 years) had typical carcinoid tumour, and 3 patients (12%; 1 male and 2 females; age range: 32–37 years) had an atypical carcinoid tumour.

Smoking

The smoking status was known for 20 patients with typical carcinoid tumour, of whom 3 (15%) were smokers. The smoking status of the other 2 patients with typical carcinoid was unknown. Two patients with atypical carcinoid tumours were non-smokers while the smoking status of the third was not known. All the smokers in this series were men.

Mode of presentation

The majority of patients in our series presented with haemoptysis ($n = 20$; 80%) and cough ($n = 16$; 64%). The other symptoms included dyspnoea ($n = 10$; 40%), chest pain ($n = 5$; 20%), SVC syndrome ($n = 1$; 4%) and fever ($n = 1$; 4%). Carcinoid syndrome was not encountered in any patient. All patients were symptomatic at the time of presentation. The symptoms and signs are summarised in Table 1.

The predominant roentgenographic findings were post-obstructive atelectasis and pneumonitis ($n = 13$; 52%), mass lesion ($n = 9$; 36%) and bronchiectasis ($n = 2$; 8%). One patient (4%) had a normal chest radiograph.

Method of diagnosis

All patients underwent diagnostic bronchoscopy. The diagnosis of carcinoid tumour was made using bronchoscopy and bronchoscopic biopsy in 23 patients (92%). Of those who underwent bronchoscopic biopsy, 12 patients (52.2%) developed moderate bleed following bronchoscopic biopsy, which was controlled by local measures. One patient had excessive bleeding during the procedure that was controlled, however, he required to be transfused later.

Tumour was not visualised by bronchoscopy in 2 patients. Of these percutaneous needle biopsy was the mode of diagnosis in 1 patient (4%); and in 1 patient (4%) diagnosis was by thoracotomy biopsy.

Tumour location

Most of the carcinoid tumours ($n = 21$; 84%) arose in the major bronchi – in 13 (52%) patients, it arose from the main-stem bronchi, and in 8 (32%) patients, it arose from lobar bronchi (Table 2). The commonest site was the right main bronchus ($n = 9$; 36%). The tumour arose from the periphery of the lungs (i.e., at the segmental bronchi or beyond) in 2 patients (8%). It presented as hilar mass in 2 patients (8%). The tumour was located in the right lung in 14 (56%) patients and in the left lung in 11 (44%) patients.

Tumour spread

Among the 17 patients with typical carcinoid group who underwent surgery, only one had mediastinal lymph node involvement as detected by mediastinal sampling at the time of surgery. Sixteen patients showed no evidence of mediastinal lymph node involvement or distant metastasis. One patient had evidence of mediastinal tumour

Table 1 Mode of presentation

Presenting symptom/sign	Patients (no.)	(%)
Haemoptysis	20	80
Cough	16	64
Breathlessness	10	40
Others		
Chest pain	5	20
Fever	1	4
SVC syndrome	1	4
Carcinoid syndrome	0	
Asymptomatic	0	
Evidence of bronchial obstruction		
Post-obstructive atelectasis and pneumonitis	13	52
Post-obstructive bronchiectasis	2	8
Mass lesions	9	36
Normal chest radiograph	1	4

Table 2 Tumour location[a]

Site	Central	Peripheral[b]	Total
Right lung	12	1	13
Main bronchus	9	—	
Intermediate bronchus	2	—	
Upper lobe	0	—	
Middle lobe	0	—	
Lower lobe	1	1	
Left lung	9	1	10
Main bronchus	4	—	
Upper lobe	0	—	
Lingula	1	—	
Lower lobe	4	1	
Hilar			2

[a] Data are presented as no.
[b] Peripheral tumours arising in the segmental bronchus or beyond.

encasement without mediastinal lymph node involvement. CT scan of the thorax was performed in 2 patients with typical carcinoid who did not undergo surgery. Mediastinal lymph node involvement was present in 1 patient and absent in one. In the remaining 3 patients mediastinal node involvement could not be assessed.

Two patients with atypical carcinoid who underwent surgery had no lymph node involvement on the basis of sampling at surgery and the third patient who did not have surgery extending up to the mediastinum on CT scan.

Immuno-histochemical findings

Information on immuno-histochemical staining was available in 22 of the 27 patients in the study. Synaptophysin was positive in 19 of the 20 specimens stained (94.7%), Chromogranin was positive in 10 of 16 specimens stained (61.8%), neuron-specific enolase (NSE) was positive in 7 of 11 specimens stained (63.6%), and cytokeratin (CK) was positive in 5 of 15 specimens stained (33.3%).

Treatment

Surgery was performed in 19 patients (76%) — pneumonectomy in 13 patients (52%) and lobectomy in 4 patients (16%). In 2 patients (8%), the tumour was considered inoperable on the operating table due to adhesions and mediastinal invasion. Five out of 25 patients (20%) refused surgery and subsequently, were lost to follow-up. Three patients (12%) underwent chemotherapy and 2 patients who had surgery (8%) also underwent adjuvant chemotherapy.

Discussion

Our female to male ratio of 0.8:1 contrasts with most other studies in the literature, which report a slight female predominance.[5–8] One study reported an equal sex ratio.[9] The relative rates of typical and atypical carcinoid tumours in our study were 88:12, which is almost similar to that reported (90:10) by Fink et al.[10] In most other studies, the prevalence of atypical carcinoids was more than 20%.[11–13] However, Hurt et al. reported a much lower prevalence of only 1% of atypical carcinoid tumours.[5]

Despite previous reports, endobronchial biopsies were quite safe in our hands without significant bleeding. When clinical features and gross bronchoscopic appearance gave rise to the suspicion of carcinoid, we always proceeded to perform biopsies after keeping 1:1000 adrenaline and ice-cold saline ready for use, if required. Almost all patients had bleeding and 52.2% of patients developed significant bleeding following endobronchial biopsies. In all cases the bleeding could be controlled before the bronchoscope was removed. In 1 patient, while the bleeding came under control, the situation was compounded by post-bronchoscopic haemoptysis and he required blood transfusion. There was no mortality.

Strictly endoluminal typical carcinoids of the lung may be amenable to bronchoscopic resection using Nd—YAG laser, photodynamic therapy, cryotherapy or brachytherapy. However, this may not be feasible in most centres since it requires expertise in interventional bronchoscopy, and this was not attempted in our patients.

All patients were symptomatic at presentation, which is probably explained by the high incidence of central tumours in our series. In 23 out of 25 patients (92%) in our series, the tumour arose from the main stem, lobar or segmental bronchi, and thus was accessible to the bronchoscope. There were only 2 cases of peripheral tumours. Most studies have shown a higher incidence of peripheral tumours.[6,10] Marty-Ane et al.[14] and McCaughan[8] found more peripheral carciniods than central carcinoids in their series of 23 and 124 patients, respectively. On the other hand, Okike et al.,[15] in their series reported that only 16% of 203 patients had peripheral carcinoid tumours. Hurt et al.[5] and Descovich et al.[16] reported high incidence of peripheral tumours of 97% and 82.8% in their series of 79 and 35 patients, respectively.

The most common site of involvement was the right main bronchus in our series. Some of the other series have found a higher incidence in other parts of bronchial tree. Ranchod and Levine[17] and Fink et al.[10] reported that the right middle lobe involvement was the commonest, while Okike et al.[15] reported that right and left lower lobe were the most commonly involved.

As in our series, the previous reports[3,8,12,18,19] have noted that the regional nodal involvement in typical carcinoid tumours was low and ranged from 3 to 20%. Unlike other series', 2 out of 3 patients with atypical carcinoids in our series had no mediastinal lymph node involvement. However, we feel that the numbers are too small to draw major conclusions.

In this series, on immuno-histochemical studies, 18/19 specimens (994.7%) stained positive for Synaptophysin, 10/16 (61.8%) for Chromogrannin and 7/11 (63.6%) for neuron-specific enolase (NSE), which is similar to other case series. However, cytokeratin (CK) was positive only in 5/15 (33.3%) unlike other series where less than 20% are cytokeratin negative.

One reason for the large number of cases with negative cytokeratin is that cytokeratin is focally expressed in neuroendocrine tumours. In this series immunohistochemistry was performed in most cases on a bronchial biopsy

Table 3 Data collected from large series in the literature

Source	Year	No.	Age	F:M	Location (%)		Histology (%)		Surgery (%)	
					Cent.	Periph.	Typ.	Atyp.	Lob.	Pneum.
Hurt et al.	1984	79	47	1.1:1	97	3	99	1	66	13
McCaughon	1985	124	55	1.2:1	37	63	81	19	42	11
Bertelsen	1985	82	45	1.1:1	79	21	79	21	54	6
Harpole et al.	1992	126	53	0.8:1	55	45	66	34	50	12
Mezzetti et al.	1995	32	50.3	1:1	62.5	37.5	84.4	15.6	NA	NA
Gould et al.	1998	87	55	0.8:1	NA	NA	74	26	69	7
Descovich	2000	35	43	1.6:1	82.8	17.2	85.7	14.3	57.1	17.1
Fink et al.	2000	142	52	1.6:1	68	32	90	10	56	16
Our study	*2008*	*25*	*38.3*	*0.8:1*	*92*	*8*	*88*	*12*	*16*	*52*

Cent — central; periph — peripheral; typ — typical; atyp — atypical; lob — lobectomy; and pneum — pneumonectomy.

which represent only a small portion of tumour. It is possible that if the stain was done on a large biopsy or resection samples, cases with positive staining for cytokeratin would increase.

Table 3 summarises 707 cases reported in the literature in the last 20 years (1984—2001) and compares these reports with our series.

Conclusion

Pulmonary carcinoid is an uncommon tumour in India and we have reported the first case series from here. It is slightly more common in men and occurs frequently in the central airways causing obstruction. Diagnosis in most cases was obtained by bronchoscopic biopsy. Surgical excision was offered to most patients, however, some of them declined this option.

Conflict of interest

This is to advise that all authors were actively in the direct care of the patient and in preparation of the manuscript. This is also to advise that there is no conflict of interest involved.

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